TSG-6 Regulates Bone Remodeling through Inhibition of Osteoblastogenesis and Osteoclast Activation

Titre	TSG-6 Regulates Bone Remodeling through Inhibition of Osteoblastogenesis and Osteoclast Activation
Type de publication	Article de revue
Auteur	Mahoney, David-J. [1], Mikecz, Katalin [2], Ali, Tariq [3], Mabilleau, Guillaume [4], Benayahu, Dafna [5], Plaas, Anna [6], Milner, Caroline-M. [7], Day, Anthony-J. [8], Sabokbar, Afsie [9]
Editeur	American Society for Biochemistry and Molecular Biology
Type	Article scientifique dans une revue à comité de lecture
Année	2008
Langue	Anglais
Date	2008/09/19
Numéro	38
Pagination	25952 - 25962
Volume	283
Titre de la revue	Journal of Biological Chemistry
ISSN	0021-9258, 1083-351X
Résumé en anglais	TSG-6 is an inflammation-induced protein that is produced at pathological sites, including arthritic joints. In animal models of arthritis, TSG-6 protects against joint damage; this has been attributed to its inhibitory effects on neutrophil migration and plasmin activity. Here we investigated whether TSG-6 can directly influence bone erosion. Our data reveal that TSG-6 inhibits RANKL-induced osteoclast differentiation/activation from human and murine precursor cells, where elevated dentine erosion by osteoclasts derived from TSG-6-/- mice is consistent with the very severe arthritis seen in these animals. However, the long bones from unchallenged TSG-6-/- mice were found to have higher trabecular mass than controls, suggesting that in the absence of inflammation TSG-6 has a role in bone homeostasis; we have detected expression of the TSG-6 protein in the bone marrow of unchallenged wild type mice. Furthermore, we have observed that TSG-6 can inhibit bone morphogenetic protein-2 (BMP-2)-mediated osteoblast differentiation. Interaction analysis revealed that TSG-6 binds directly to RANKL and to BMP-2 (as well as other osteogenic BMPs but not BMP-3) via composite surfaces involving its Link and CUB modules. Consistent with this, the full-length protein is required for maximal inhibition of osteoblast differentiation and osteoclast activation, although the isolated Link module retains significant activity in the latter case. We hypothesize that TSG-6 has dual roles in bone remodeling; one protective, where it inhibits RANKL-induced bone erosion in inflammatory diseases such as arthritis, and the other homeostatic, where its interactions with BMP-2 and RANKL help to balance mineralization by osteoblasts and bone resorption by osteoclasts.
URL de la notice	http://okina.univ-angers.fr/publications/ua3290 [10]

DOI	10.1074/jbc.M802138200 [11]
Lien vers le document	http://dx.doi.org/10.1074/jbc.M802138200 [11]

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